REMARKS/ARGUMENTS

Applicants have carefully considered this Application in connection with the Examiner's Action, and respectfully request reconsideration of this Application in view of the above Amendment and the following remarks.

Claims 110-129 are pending in the application. Claims 1-109 were previously cancelled. New Claims 128 and 129 have been added.

Claims 110 and 111 have been amended to provide that the method is for designing a preferred oligonucleotide sequence. Claims 110 and 111 have also been amended so that modified oligonucleotide sequences are created that correspond to the original oligonucleotide sequence and have a modified base. The step of calculating the duplex stability (or melting temperature) is of the modified oligonucleotide sequences containing the at least one modified base. The preferred oligonucleotide sequence having the selected duplex stability (or melting temperature) of the modified oligonucleotide sequences is then selected. As a final step, the step of creating an oligonucleotide comprising the preferred oligonucleotide sequence has been added.

New Claims 128 and 129 have also been added to provide that the oligonucleotide sequences of Claims 110 and 111 already include one universal base and that the modified oligonucleotide sequences created contain that universal base and one additional modified base.

Support for these amendments can be found in the specification, particularly at Page 45, lines 2-13, Example 13 and Table 6. Page 45, lines 2-5 notes that "T_ms of multiple modified oligonucleotides [i.e., containing at least one modified base] containing the same number of bases are leveled using an algorithm to select nearest neighbor parameters from any combination of normal bases [and additional modified bases]." Page 45, lines 11-12 states that "[i]n some instances, modified bases are used that improve duplex stability in addition to those modified bases that decrease duplex stability." As stated at Page 87, lines 13-24, the algorithm is used to generate data containing predictions of the T_m of oligonucleotide sequences containing modified bases and in some cases an MGB. As stated at Page 89, lines 4-6, "[u]sing the algorithm above, and information from the nearest-neighbor parameters, a collection of probe or primer sequences

with the desired T_ms can be calculated." Table 5 illustrates the addition of modified bases to increase duplex stability of an oligonucleotide sequence already containing a universal base. Table 6 illustrates a wide variety of oligonucleotide sequences that could be used to generate a calculated oligonucleotide sequence. Those skilled in the art are well-acquainted with the process for generating an oligonucleotide having a desired sequence, as further described in the specification at Page 10, line 31 – Page 12, line 3.

Applicant has also amended Claims 110, 111, and 118 to delete "universal base."

Additional claims have been amended to address the Examiner's concerns regarding punctuation and grammar, among other issues discussed more fully below.

I. Status of the Claims

Applicant notes that Claims 110-127 are pending, Claims 110-127 stand rejected to, and Claims 110, 111, 114, 119, 121, and 126 stand objected to.

II. Priority

Applicant notes that the Examiner maintains a refusal to grant priority to application Serial Nos. 09/640953, 09/054832, 09/431385, and 09/054830. Applicants do not acquiesce in this decision but nevertheless for the sake of advancing prosecution will adhere to the priority date of the current application being November 28, 2000.

III. Terminal Disclaimer

Applicant thanks the Examiner for indicating that the previously-submitted terminal disclaimer has been accepted and recorded.

IV. Claim Objections

Claims 110, 111, 114, 119, 121, and 124 stand objected to for listing members of a group without a comma between the last two members. Applicant has amended these claims according to the Examiner's suggestion and requests withdrawal of these objections.

Claim 126 stands objected to for the omission of the term "has." Applicant has amended this claim according to the Examiner's suggestion and requests withdrawal of this objection.

V. Claim Rejections – 35 U.S.C. §101

Claims 110-127 stand rejected under 35 U.S.C. § 101 for being drawn to non-statutory subject matter. The Examiner asserts that the claims are drawn to a process that is not statutory subject matter because it is not tied to a machine or apparatus and does not transform an article into a different state or thing. *See In re Bilski*, 88 U.S.P.Q.2d 1385 (Fed. Cir. 2008).

Applicant has amended Claims 110 and 111 to address the Examiner's concerns. In particular, Claims 110 and 111 now require the step of creating an oligonucleotide having the preferred oligonucleotide sequence. Thus, after the steps of the process are used to generate a preferred oligonucleotide sequence having the desired duplex stability, an actual oligonucleotide is created comprising the preferred oligonucleotide sequence. This oligonucleotide represents a transformed article that is created using the claimed process.

Applicant respectfully submits that, in view of these amendments, Claims 110-127 are patentable under 35 U.S.C. § 101 for being directed to statutory subject matter.

VI. Claim Rejections – 35 U.S.C. § 112

Claims 110-127 stand rejected under 35 U.S.C. § 112, second paragraph, for being indefinite. The Examiner notes that Claims 110-123, 126, and 127 are indefinite because it is not clear if an oligonucleotide molecule or data of a sequence of an oligonucleotide is referred to in the first step of Claims 110 and 111. Claims 124 and 124 are said to be indefinite because they require the presence of physical molecules used in hybridization procedures or an array apparatus.

Applicant has amended Claims 110 and 111 to clarify that steps a), b), c), and d) of these claims require an oligonucleotide sequence. Step e), which has been added, requires the creation of an oligonucleotide molecule. Thus, Claims 124 and 125 refer to the oligonucleotide created in step e) while the other steps refer to the data of an oligonucleotide sequence.

In view of these amendments, Applicant respectfully requests that the rejections of Claims 110-127 under 35 U.S.C. § 112, second paragraph, be withdrawn.

VII. Claim Rejections – 35 U.S.C. § 103

A. Schutz in view of Martin et al. and in further view of Loakes et al.

Claims 110, 112, 113, 118, 123, and 124 stand rejected under 35 U.S.C. § 103(a) for being obvious in view of Schutz et al. (Biotechniques December 1999) ("Schutz") combined with Martin ct al. (Nucleic Acids Research 1985) ("Martin") and Loakes et al. (Nucleic Acids Research 1995) ("Loakes"). The Examiner asserts that Schutz teaches a computer-mediated method for calculating the T_m of input oligonucleotide sequences. While the Examiner notes that Schutz does not show calculation of the T_m for oligonucleotide sequences containing modified bases, the Examiner asserts that Martin discloses the use of deoxyinosine and the calculation of nearest neighbor thermodynamic parameters. Finally, Loakes is cited for its asserted teachings regarding deoxyinosine being a universal base. The Examiner asserts that integrating deoxyinosine into the method of Schutz would require only routine substitution. Applicant respectfully disagrccs and asserts that the claims are patentable over these references.

Applicant respectfully asserts that Schutz in combination with Martin and Loakes does not teach or suggest all of the limitations of the claims as amended. Claims 110, 111, and 118 have been amended to delete "universal base." Thus, the claims require the inclusion of at least one modified base in the oligonucleotide sequence that cannot be a universal base. It has already been cstablished that Schutz is silent with regard to the use of modified bases. Furthermore, Martin and Loakes are citcd for teaching universal bascs. Neither Schutz, Martin, nor Loakes teach or suggest the inclusion of the claimed modified bases, namely, unsubstituted pyrazolo[3,4-d]pyrimidines, 3-substituted pyrazolo[3,4-d]pyrimidincs, and 5-substituted pyrimidines. For that reason, these references in combination cannot render the claims obvious.

In addition, evcn prior to amendment, the claims have always requirecl more than simple calculation of thc melting temperatures of oligonucleotides, as Schutz teaches. The claims have always required designing a modified oligonucleotide having a selected duplex stability. As the title to the application suggests, the methods are directed to T_m leveling, not simply to T_m

calculation. The amendments to the claims better clarify the steps involved in this T_m leveling. This claimed T_m leveling requires the theoretical insertion of at least one modified base into an oligonucleotide sequence, the calculation of the T_m or duplex stability of each one, and the selection of the sequence containing at least one modified base that provides the desired duplex stability. Schutz does not provide this teaching, as Schutz does not teach substitution of modified bases. Schutz also admits that its teachings are limited with regard to dangling ends and double and terminal mismatches, and presumably to minor groove binders, because thermodynamic data was not published for any of these features. Finally, Schutz is entirely silent with regard to the concept that an oligonucleotide having desired duplex stability can be created through the insertion of at least one modified base, in conjunction with a thermodynamic analysis of the various permutations.

It is noted that new Claims 128 and 129 have been added in which the oligonucleotide sequence contains a universal base. While Martin and Loakes may suggest the use of universal bases, these references do not disclose modified oligonucleotide sequences containing at least one modified base (that is not a universal base) in addition to the universal base of the original oligonucleotide sequence. None of the cited references suggest that additional modified bases (that are not universal bases) can assist in determining a preferred oligonucleotide sequence having a desired duplex stability. This concept is part of the T_m leveling methods to which these claims are directed.

For these reasons, Applicant respectfully submits that Claims 110, 112, 113, 118, 123, and 124, as well as Claims 128 and 129, are patentable over the combined teachings of Schutz, Martin, and Loakes.

B. Schutz in view of Martin and Loakes and in further view of Kutyavin

Claims 110-113, 118-121, 123, and 124 stand rejected under 35 U.S.C. § 103(a) as being obvious over Schutz in view of Martin and Loakes and in further view of Kutyavin (Nucleic Acids Research 1997) ("Kutyavin"). The Examiner asserts that in addition to the teachings of Schutz, Martin, and Loakes applied to the underlying claims, Kutyavin teaches the use of deoxyinosine (a universal base) and a minor groove binder. Applicant respectfully disagrees and asserts that the claims are patentable over these references.

As already discussed above, Applicant notes that Claims 110 and 111 have been amended to remove "universal bases" from the list of modified bases. Thus, the teachings of Martin and Loakes cannot be applied to the claims. Further, these references do not provide any teachings of other claimed modified bases. The same is true of Kutyavin. While Kutyavin may disclose oligonucleotides containing deoxyinosine and a minor groove binder, it does not contain any teachings with regard to the use of the claimed modified bases. Furthermore, it provides no teachings with regard to the inclusion of at least one modified base in order to obtain an oligonucleotide sequence having a desired duplex stability. The process of substituting various possible modified bases into the original oligonucleotide sequence and determining the one that has the desired duplex stability is not discussed or suggested in any of these references. Thus, Kutyavin does not cure the fact that Schutz, Martin, and Loakes do not teach or suggest the claimed method of T_m leveling using modified bases.

For these reasons, Claims 110-113, 118-121, 123, and 124, as well as new Claims 128 and 129, are patentable over Schutz in view of Martin and Loakes and in further view of Kutyavin.

C. Schutz in view of Martin and Loakes and in further view of Singh et al.

Claims 110, 111, 114, 116, 117, and 127 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Schutz in view of Martin and Loakes and in further view of Singh et al. (Chemical Communications 1998) ("Singh"). The Examiner asserts that in addition to the teachings of Schutz, Martin, and Loakes applied to the underlying claims, Singh teaches the use of locked sugars to increase oligonucleotide melting temperatures. Applicant respectfully disagrees and asserts that the claims are patentable over these references.

As already discussed above, Applicant notes that Claims 110 and 111 have been amended to remove "universal bases" from the list of modified bases. Thus, the teachings of Martin and Loakes cannot be applied to the claims. Further, these references do not provide any teachings of the claimed modified bases. The same is true of Singh. Singh may disclose teachings of the use of locked sugars in oligonucleotides, but it does not contain any teachings with regard to the use of the claimed modified bases. Furthermore, while Singh may discuss the increase in melting temperature due to the use of locked sugars, Singh provides no teachings with regard to

the inclusion of at least one modified base in order to obtain an oligonucleotide sequence having a desired duplex stability. The process of substituting various possible modified bases into the original oligonucleotide sequence and determining the one that has the desired duplex stability is not discussed or suggested in any of these references. Thus, Singh also does not cure the fact that Schutz, Martin, and Loakes do not teach or suggest the claimed method of T_m leveling.

For these reasons, Claims 110, 111, 114, 116, 117, and 127, as well as new Claims 128 and 129, are patentable over Schutz in view of Martin and Loakes and in further view of Singh.

D. Schutz in view of Martin and Loakes in further view of Griffin et al.

Claims 110, 111, 114, and 115 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Schutz in view of Martin and Loakes and in further view of Griffin et al. (Analytical Biochemistry 1998) ("Griffin"). The Examiner asserts that in addition to the teachings of Schutz, Martin, and Loakes applied to the underlying claims, Griffin teaches the use of a peptide nucleic acid backbone and its advantages of higher stabilities when hybridized to DNA. Applicant respectfully disagrees and asserts that the claims are patentable over these references.

As already discussed, Applicant notes that Claims 110 and 111 have been amended to remove "universal bases" from the list of modified bases. Thus, the teachings of Martin and Loakes cannot be applied to the claims. Further, these references do not provide any teachings of the claimed modified bases. The same is true of Griffin. Griffin may disclose teachings of the use of a peptide nucleic acid backbone in oligonucleotides, but it does not contain any teachings with regard to the use of the claimed modified bases. Furthermore, while Griffin may discuss methods for calculating melting temperature and duplex stability, Griffin provides no teachings with regard to the inclusion of at least one modified base in order to obtain an oligonucleotide sequence having a desired duplex stability. The fact that peptide nucleic acids might produce higher stabilities when hybridized to DNA does not suggest the method of T_m leveling required by the claims. Considering the absence of teachings regarding the insertion of modified bases to level the T_m and produce a desired duplex stability, the cited references in combination do not teach or suggest the claimed subject matter.

For these reasons, Claims 110, 111, 114, and 115, as well as new Claims 128 and 129, are patentable over Schutz in view of Martin and Loakes and in further view of Griffin.

E. Schutz in view of Martin and Loakes in further view of Lizardi et al.

Claims 110, 111, and 125 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Schutz in view of Martin and Loakes and in further view of Lizardi et al. (U.S. Patent No. 6403319) ("Lizardi"). The Examiner asserts that in addition to the teachings of Schutz, Martin, and Loakes applied to the underlying claims, Lizardi teaches the use of capture probes and the calculation of their duplex stability. Applicant respectfully disagrees and asserts that the claims are patentable over these references.

As already discussed, Claims 110 and 111 have been amended to remove "universal bases" from the list of modified bases. Thus, the teachings of Martin and Loakes cannot be applied to the claims. Further, these references do not provide any teachings of the claimed modified bases. The same is true of Lizardi. Lizardi may disclose teachings of detector probes used to capture other nucleic acid molecules and the calculation of duplex stability, but it does not contain any teachings with regard to the use of the claimed modified bases to obtain an oligonucleotide sequence having a preferred duplex stability. Considering the absence of teachings regarding the insertion of modified bases to level the T_m and produce a desired duplex stability, the cited references in combination do not teach or suggest the claimed subject matter.

For these reasons, Claims 110, 111, and 125, as well as new Claims 128 and 129, are patentable over Schutz in view of Martin and Loakes and in further view of Lizardi.

F. Schutz in view of Martin and Loakes in further view of Kutyavin et al.

Claims 110, 119, 120, and 122 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Schutz in view of Martin and Loakes and in further view of Kutyavin et al. (Nucleic Acids Research 2000) ("Kutyavin '00"). The Examiner asserts that in addition to the teachings of Schutz, Martin, and Loakes applied to the underlying claims, Kutyavin '00 teaches the use of a minor groove binder linked by a quencher molecule. Applicant respectfully disagrees and asserts that the claims are patentable over these references.

As already discussed, Claim 110 has been amended to remove "universal bases" from the list of modified bases. Thus, the teachings of Martin and Loakes cannot be applied to the claims. Further, these references do not provide any teachings of the claimed modified bases. The same is true of Kutyavin '00. Kutyavin '00's teachings are limited to those regarding minor groove binders linked by quenchers and cannot cure the absence of the teaching of the use of modified bases in the claimed method. The cited references in combination do not contain any teachings with regard to the use of the claimed modified bases to create modified oligonucleotide sequences and obtain an oligonucleotide sequence having a preferred duplex stability. Considering the absence of teachings regarding the insertion of modified bases to level the T_m and produce a desired duplex stability, the cited references in combination do not teach or suggest the claimed subject matter.

For these reasons, Claims 110, 119, 120, and 122 are patentable over Schutz in view of Martin and Loakes and in further view of Kutyavin '00.

G. Schutz in view of Martin and Loakes and Griffin and in further view of Kutyavin et al.

Claims 110, 111, 114, 115, and 126 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Schutz in view of Martin and Loakes and Griffin and in further view of Kutyavin et al. (Nucleic Acids Research 2000) ("Kutyavin '00"). The Examiner asserts that in addition to the teachings of Schutz, Martin, and Loakes, applied to the underlying claims, Griffin teaches the use of a peptide nucleic acid backbone and Kutyavin '00 teaches the use of a minor groove binder linked by a quencher molecule. Applicant respectfully disagrees and asserts that the claims are patentable over these references.

As already discussed, Claims 110 and 111 have been amended to remove "universal bases" from the list of modified bases. Thus, the teachings of Martin and Loakes cannot be applied to the claims. Further, these references do not provide any teachings of the claimed modified bases. The same is true of Griffin and Kutyavin '00. Griffin's teachings may pertain to peptide nucleic acid backbones and Kutyavin '00's teachings may relate to minor groove binders linked by quenchers, but these teachings combined cannot cure the absence of the teaching of the use of modified bases in the claimed method. The cited references in

combination do not contain any teachings with regard to the use of the claimed modified bases in modified oligonucleotide sequences to obtain an oligonucleotide sequence having a preferred duplex stability. Considering the absence of teachings regarding the insertion of additional modified bases to level the T_m and produce a desired duplex stability, the cited references in combination do not teach or suggest the claimed subject matter.

For these reasons, Claims 110, 111, 114, 115, and 126, and new Claims 128 and 129, are patentable over Schutz in view of Martin and Loakes and Griffin and in further view of Kutyavin '00.

VIII. Double Patenting

Applicant wishes to thank the Examiner for indicating that the provisional rejection of Claims 110-116 and 118-121 under the doctrine of obviousness-type double patenting is withdrawn.

CONCLUSION

In view of the foregoing remarks and for various other reasons readily apparent, Applicants submit that all of the claims now present are allowable, and withdrawal of the rejections and a Notice of Allowance are courteously solicited.

If any impediment to the allowance of the claims remains after consideration of this amendment, a telephone interview with the Examiner is hereby requested by the undersigned at (214) 953-5758 so that such issues may be resolved as expeditiously as possible.

A request for a four month extension of time is submitted with this request, along with the extension fee and the fee for filing an RCE. The Commissioner is hereby authorized to charge any fee or credit any refund to Deposit Account No. 10-0096.

Dated: 11/13/09

Respectfully submitted,

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